

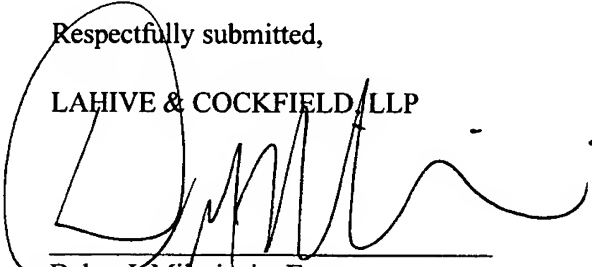
REMARKS

The claims have been amended as to form (*e.g.*, to correct improper dependencies). Attached hereto is APPENDIX A which contains a marked-up version of the changes made to the claims by the instant amendment. The attached appendix is captioned "Version With Markings to Show Changes Made". Support for the claim amendments can be found, for example, in the claims as originally filed. No new matter has been added.

Applicants respectfully submit that the above-identified application is in condition for allowance. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,

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APPENDIX A
VERSION WITH MARKINGS TO SHOW CHANGES MADE

15. (Amended) The light chain of any one claims [1, 3, 4, 6, 8, 10, 11 and 13] 1, 6, and 13, wherein the human acceptor light chain is of the subtype kappa II (Kabat convention).

16. (Amended) The heavy chain of any one claims [2, 5, 7, 9, 12 and 14] 2, 7, and 14, wherein the human acceptor heavy chain is of the subtype III (Kabat convention).

21. (Amended) The light chain of any one of claims [1, 3, 4, 6, 8, 10, 11, 13, 15, 17 and 18] 1, 6, and 13, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable light chain sequences at that position.

22. (Amended) The light chain of claim [1, 3, 4, 6, 8, 10, 11, 13, 15, 17 and 18] 1, 6, and 13, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable light chain sequence.

24. (Amended) The heavy chain of any one of claims [2, 5, 7, 9, 12, 14, 16, 19 and 20] 2, 7, and 14, wherein at least one rare human framework residue is substituted with an amino acid residue which is common for human variable heavy chain sequences at that position.

25. (Amended) The heavy chain of any one of claims [2, 5, 7, 9, 12, 14, 16, 19 and 20] 2, 7, and 14, wherein at least one rare human framework residue is substituted with a corresponding amino acid residue from a germline variable heavy chain sequence.

28. (Amended) The light chain of [any one of claims 21-23] 21, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human light chain variable region sequences in the light chain variable region subgroup, and the

common residue is selected based on an occurrence at that position in greater than 50% of sequences in the light chain variable region subgroup.

29. (Amended) The heavy chain of [any one of claims 24-26] 24, wherein the rare framework residue is selected based on occurrence at that position in less than 10% of human heavy chain variable region sequences in the heavy chain variable region subgroup, and the common residue is selected based on an occurrence at that position in greater than 50% of sequences in the heavy chain variable region subgroup.

32. (Amended) A humanized immunoglobulin [comprising the light chain of any one of claims 1, 3, 4, 6, 8, 10, 11, 13, 15, 17 and 18, and the heavy chain of any one of claims 2, 5, 7, 9, 12, 14, 16, 19 and 20,] comprising a light chain selected from the group consisting of:

- (a) a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and comprising variable framework regions from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is selected from the group consisting of
 - (i) a residue that non-covalently binds antigen directly;
 - (ii) a residue adjacent to a CDR;
 - (iii) a CDR-interacting residue; and
 - (iv) a residue participating in the VL-VH interface;
- (b) a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and comprising variable framework regions from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework

residue is a residue capable of affecting light chain variable region conformation or function as identified by analysis of a three-dimensional model of the variable region;

- (c) a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and a variable framework regions from a human acceptor immunoglobulin light chain, provided that at least one framework residue selected from the group consisting of L1, L2, L36 and L46 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence; and
- (d) a light chain comprising the complementarity determining regions (CDRs) and variable region framework residues L1, L2, L36 and L46 (Kabat numbering convention) from the monoclonal antibody 3D6 light chain, wherein the remainder of the light chain is from a human immunoglobulin;

and a heavy chain selected from the group consisting of:

- (a) heavy chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and comprising variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is selected from the group consisting of:

 - (i) a residue that non-covalently binds antigen directly;
 - (ii) a residue adjacent to a CDR;
 - (iii) a CDR-interacting residue; and
 - (iv) a residue participating in the VL-VH interface;
- (b) a heavy chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and comprising variable framework regions from a human

- acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is a residue capable of affecting heavy chain variable region conformation or function as identified by analysis of a three-dimensional model of the variable region;
- (c) a heavy chain comprising variable region complementarity determining regions from the 3D6 heavy chain variable region sequence set forth as SEQ ID NO:4, and a variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue selected from the group consisting of H49, H93 and H94 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence; and
- (d) a heavy chain comprising the complementarity determining regions (CDRs) and variable framework residues H49, H93 and H94 (Kabat numbering convention) from the monoclonal antibody 3D6 heavy chain, wherein the remainder of the heavy chain is from a human immunoglobulin;
- or an antigen binding fragment of said immunoglobulin.

49. (Amended) A humanized [antibody] immunoglobulin comprising the complementarity determining regions (CDR1, CDR2 and CDR3) of the 3D6 variable light chain sequence set forth as SEQ ID NO:2.

50. (Amended) A humanized [antibody] immunoglobulin comprising the complementarity determining regions (CDR1, CDR2 and CDR3) of the 3D6 variable heavy chain sequence set forth as SEQ ID NO:4.

51. (Amended) A humanized [antibody] immunoglobulin, or antigen-binding fragment thereof, which specifically binds to beta amyloid peptide (A β), comprising a variable region

comprising complementarity determining regions (CDRs) corresponding to CDRs from the mouse 3D6 [antibody] immunoglobulin.

52. (Amended) A humanized [antibody] immunoglobulin which binds beta amyloid peptide (A β) with an affinity of at least 10^7 M⁻¹ comprising:

- (a) a light chain variable domain comprising murine 3D6 complementarity determining region (CDR) amino acid residues and human VL subgroup II variable domain framework region (FR) amino acid residues; and
- (b) a heavy chain variable domain comprising murine 3D6 complementarity determining region (CDR) amino acid residues and human VH subgroup III variable domain framework region (FR) amino acid residues.

58. (Amended) A method of preventing or treating an amyloidogenic disease in a patient, comprising administering to the patient an effective dosage of the [humanized] immunoglobulin of any one of claims [32-52] 32, 42 and 49-52.

59. (Amended) A method of preventing or treating Alzheimer's disease in a patient, comprising administering to the patient an effective dosage of the [humanized] immunoglobulin of any one of claims [32-52] 32, 42 and 49-52.

60. (Amended) The method of claim 59, wherein the effective dosage of [humanized] immunoglobulin is 1 mg/kg body weight.

61. (Amended) The method of claim 59, wherein the effective dosage of [humanized] immunoglobulin is 10 mg/kg body weight.

62. (Amended) A pharmaceutical composition comprising the immunoglobulin of any one of claims [32-52] 32, 42 and 49-52 and a pharmaceutical carrier.

63. (Amended) An isolated polypeptide selected from the group consisting of;
- (a) a polypeptide comprising a fragment of SEQ ID NO:2 selected from the group consisting of amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2[.];
 - (b) a polypeptide comprising amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2;
 - (c) a polypeptide comprising a fragment of SEQ ID NO:4 selected from the group consisting of amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 99-107 of SEQ ID NO:4;
 - (d) a polypeptide comprising amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 99-107 of SEQ ID NO:4;
 - (e) a polypeptide comprising the amino acid sequence of SEQ ID NO:2;
 - (f) a polypeptide comprising the amino acid sequence of SEQ ID NO:4; and
 - (g) a polypeptide comprising residues 1-112 of the amino acid sequence of SEQ ID NO:2 or comprising residues 1-119 of the amino acid sequence of SEQ ID NO:4.
72. (Amended) An isolated nucleic acid molecule [encoding the light chain of any one of claims 1, 3, 4, 6, 8, 10, , 11, 13, 15, 17 and 18] selected from the group consisting of:
- (a) a nucleic acid molecule encoding a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and comprising variable framework regions from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is selected from the group consisting of:
 - (i) a residue that non-covalently binds antigen directly;
 - (ii) a residue adjacent to a CDR;
 - (iii) a CDR-interacting residue; and
 - (iv) a residue participating in the VL-VH interface;

- (b) a nucleic acid molecule encoding a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and comprising variable framework regions from a human acceptor immunoglobulin light chain sequence, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence, wherein the framework residue is a residue capable of affecting light chain variable region conformation or function as identified by analysis of a three-dimensional model of the variable region;
- (c) a nucleic acid molecule encoding a light chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin light chain variable region sequence set forth as SEQ ID NO:2, and a variable framework regions from a human acceptor immunoglobulin light chain, provided that at least one framework residue selected from the group consisting of L1, L2, L36 and L46 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 light chain variable region sequence;
- (d) a nucleic acid molecule encoding a light chain comprising the complementarity determining regions (CDRs) and variable region framework residues L1, L2, L36 and L46 (Kabat numbering convention) from the monoclonal antibody 3D6 light chain, wherein the remainder of the light chain is from a human immunoglobulin;
- (e) a nucleic acid molecule encoding a heavy chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and comprising variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is selected from the group consisting of:
 - (i) a residue that non-covalently binds antigen directly;
 - (ii) a residue adjacent to a CDR;

- (iii) a CDR-interacting residue; and
 - (iv) a residue participating in the VL-VH interface;
- (f) a nucleic acid molecule encoding a heavy chain comprising variable region complementarity determining regions (CDRs) from the 3D6 immunoglobulin heavy chain variable region sequence set forth as SEQ ID NO:4, and comprising variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence, wherein the framework residue is a residue capable of affecting heavy chain variable region conformation or function as identified by analysis of a three-dimensional model of the variable region;
- (g) a nucleic acid molecule encoding a heavy chain comprising variable region complementarity determining regions from the 3D6 heavy chain variable region sequence set forth as SEQ ID NO:4, and a variable framework regions from a human acceptor immunoglobulin heavy chain, provided that at least one framework residue selected from the group consisting of H49, H93 and H94 (Kabat numbering convention) is substituted with the corresponding amino acid residue from the mouse 3D6 heavy chain variable region sequence;
- (h) a nucleic acid molecule encoding a heavy chain comprising the complementarity determining regions (CDRs) and variable framework residues H49, H93 and H94 (Kabat numbering convention) from the monoclonal antibody 3D6 heavy chain, wherein the remainder of the heavy chain is from a human immunoglobulin;
- (i) a nucleic acid molecule encoding a polypeptide comprising amino acids 24-39 of SEQ ID NO:2, amino acids 55-61 of SEQ ID NO:2 and amino acids 94-102 of SEQ ID NO:2;
- (j) a nucleic acid molecule encoding a polypeptide comprising a fragment of SEQ ID NO:4 selected from the group consisting of amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 94-102 of SEQ ID NO:4;

- (k) a nucleic acid molecule encoding a polypeptide comprising amino acids 31-35 of SEQ ID NO:4, amino acids 50-66 of SEQ ID NO:4 and amino acids 94-102 of SEQ ID NO:4;
- (l) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2;
- (m) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4;
- (n) nucleic acid molecule encoding a variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, said variant comprising at least one conservative amino acid substitution, wherein the variant retains the ability to direct specific binding to beta amyloid peptide (A β) with a binding affinity of at least 10^{-7} M;
- (o) nucleic acid molecule encoding a variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:4, said variant comprising at least one conservative amino acid substitution, wherein the variant retains the ability to direct specific binding to beta amyloid peptide (A β) with a binding affinity of at least 10^{-7} M;
- (p) a nucleic acid molecule encoding a polypeptide comprising residues 1-112 of the amino acid sequence of SEQ ID NO:2 or comprising residues 1-119 of the amino acid sequence of SEQ ID NO:4; and
- (q) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1 or 3.

77. (Amended) A vector comprising the nucleic acid molecule of [any of claims 72-76] claim 72.

78. (Amended) A host cell comprising the [nucleic acid molecule of any of claims 72-76] vector of claim 77.

79. (Amended) A method of producing an antibody, or fragment thereof, comprising culturing the host cell of claim [45] 78 under conditions such that the antibody or fragment is produced and isolating said antibody or fragment from the host cell or culture.

114. (Amended) A humanized immunoglobulin comprising the light chain of [any one of claims 84, 86-88, 92, 94 and 96-98] claim 84 and the heavy chain of [any one of claims 85, 89-91, and 93 and 99-101] claim 85, or antigen-binding fragment of said immunoglobulin.

133. (Amended) A method of preventing or treating an amyloidogenic disease in a patient, comprising administering to the patient an effective dosage of the humanized immunoglobulin of [any one of claims 114-131] claim 114 or 123.

137. (Amended) A pharmaceutical composition comprising the immunoglobulin of [any one of claims 114-131] claim 114 or 123 and a pharmaceutical carrier.

147. (Amended) An isolated nucleic acid molecule encoding the light chain of [any one of claims 84, 86-88, 92, 94 and 96-98] claim 84.

148. (Amended) An isolated nucleic acid molecule encoding the heavy chain of [any one of claims 85, 89-91, 93 and 99-101] claim 85.

150. (Amended) An isolated nucleic acid molecule encoding the immunoglobulin of [any one of claims 114-132] claim 114 or 123.

152. (Amended) A vector comprising the nucleic acid molecule of [any of claims 147-151] claim 150.

153. A host cell comprising [the nucleic acid molecule of any of claims 147-151] the vector of claim 152.